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THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

April 9, 1999

E. EDWARD KAVANAUGH
PRESIDENT

Mr. Robert Sherman
Food and Drug Administration (HFD-560)
Center for Drug Evaluation and Research
Office of Over-The-Counter Drug Evaluation
9201 Corporate Blvd.
Rockville, MD 20850

RE: USP Reference Standards for OTC Anticaries Dentifrice Products

Dear Mr. Sherman:

As an addendum to our letter on the above referenced subject, dated March 12, 1998 (copy attached), the changes noted in the Sodium Monofluorophosphate/Dicalcium Phosphate reference standard are supported by animal studies, in addition to those studies and analyses initially reported (fluoride uptake, RES, pH, specific gravity, available fluoride, and storage evaluations). The reference to animal studies was inadvertently left out of the March 12, 1998 letter.

Thus, those minor changes reflected in the current reference standards, noted in the March 12, 1998 letter, are all supported by the full complement of bioequivalency tests.

Also, for Monofluorophosphate/Calcium Carbonate, the fluoride concentration has been 1100 ppm since the inception of the USP reference standard program and will continue to be at this concentration level in the future.

If you have any questions, please don't hesitate to contact me.

Sincerely,

G.N. McEwen, Jr., Ph.D., J.D.
Vice President - Science

GNM/jmm

Attachment

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THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

March 12, 1998

Mr. Robert Sherman (HFD-560)
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Over-The-Counter Drug Evaluation
9201 Corporate Blvd.
Rockville, MD 20850

E. EDWARD KAVANAUGH
PRESIDENT

RE: USP Reference Standards for OTC Anticaries Dentifrice Products

Dear Mr. Sherman:

At the commencement of the cooperative FDA/industry program on reference standards and fluoride bioequivalency testing in 1978, the manufacturers recognized that of necessity, reference formulations could change in the future. To ensure fluoride reference standards of the highest potency, the manufacturers committed to a program, wherein, no fluoride reference formulation would change if it were not at least equal to the original clinically tested formula. At the same time, in fairness to those who will use the reference standards in formulation testing, the changed reference standard cannot perform significantly better than the original formula. We can assure the FDA that that principle has been strictly adhered to.

In 1993, the FDA discussed with industry representatives that the availability of ingredients and manufacturing methods could affect the availability of reference standards for use in the OTC Anticaries Dentifrice profiles testing program. Questions were raised at that time regarding one abrasive/active ingredient system. Unfortunately, this standard had to be removed from consideration because its abrasive was no longer available and an alternate grade of this abrasive would have been a major formulation change not covered by caries data.

In further discussions, it was recognized that minor modifications might be made that would have no impact on a formulation's safety or efficacy, and then the question became what testing, if any, would be needed to qualify such formulation changes. This subject has been considered by the CTFA/NDMA OTC Dentifrice Task Force.

The Task Force agrees that any change in reference standard should be qualified against the existing standard it will be replacing. Such changes may include, but are not necessarily limited to, minor manufacturing changes, such as: changes in suppliers for raw materials, which would be validated per cGMP against the existing raw material component without final formulation testing; changes in manufacturing process such as replacement machinery, which would be validated per cGMP principles without final formulation testing;

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etc. On the other hand, some changes may not be minor, such as relative amounts of processing aids. Here, qualification will include studies on fluoride uptake, enamel solubility reduction, animal caries, and available fluoride. The Task Force anticipates that future changes in the dentifrice reference standards will not be frequent.

The following lists those changes in reference standards that have occurred since the original formulations were reported some 20 years ago.

Sodium Fluoride/Sodium Bicarbonate (Powdered) Reference Standard

There has been a change in the drying agent, and a minor change in its percentage concentration resulting from the new agent's differing drying efficacy. A fluoride uptake test and a rat caries test show no difference from the previous standard, and there is no change in the pH, specific gravity, available fluoride, or storage characteristics. In addition, there is no change in moisture binding capacity and moisture, and the poured bulk density has not changed.

Sodium Fluoride Silica Reference Standard

Relative amounts of flavor components have changed, and one of the original two humectants has been eliminated with a resulting change in water content (to q.s.). These changes were done for formulation simplification and aesthetic purposes. The changes are supported by fluoride uptake and rat carie studies, as well as pH, specific gravity, available fluoride, and storage evaluations.

Sodium Monofluorophosphate/Calcium Carbonate Reference Standard

Flavor components and processing aids have been changed slightly for aesthetics and ease of manufacturing. The changes are supported by fluoride uptake, RES, and animal studies, as well as pH, specific gravity, available fluoride, and storage evaluations.

Sodium Monofluorophosphate/Dicalcium Phosphate Reference Standard

A reduction in the level of flavor components and removal of the preservative in the original formulation are the changes that have occurred in this reference standard. It was discovered that the preservative was not needed for the pH of this product. The changes are supported by fluoride uptake and RES studies, as well as pH, specific gravity, available fluoride, and storage evaluations.

Sodium Monofluorophosphate (1,000 ppm F□)/Silica Reference Standard and Sodium Monofluorophosphate (1,500 ppm F□)/Silica Reference Standard

These formulations have not changed.

Stannous Fluoride/Silica

This formulation has also changed from a two-humectant system to one humectant to simplify the formulation. This change is validated by fluoride uptake and RES studies, and animal studies, as well as matching physical properties to pH, specific gravity, available fluoride, and storage conditions. Additionally, a change in gum from carrageenan to Carboxy Methyl Cellulose was done for this reference standard. There is no potential for a Fluoride-CMC interaction and the manufacturer has extensive knowledge of CMC in dentifrice formulations that were clinically tested. Because of the change from carrageenan to CMC, KOH was eliminated from the formulation, as it was no longer needed to thicken the gum. In addition, there was a minor change in flavor, but this change was within the variation in currently marketed products.

If FDA has any questions regarding these changes, or the data supporting them, the reference standard providers are prepared to discuss them on an individual basis.

In the future, the reference suppliers agree that changes to the reference standards will be made only when necessary, and that they will be supported by all three laboratory tests, stability tests, and matching of the physical properties, (pH, specific gravity, and available fluoride).

If you have any questions of a general nature, please don't hesitate to contact me at your convenience.

Sincerely,

G.N. McEwen, Jr., Ph.D., J.D.
Vice President - Science

GNM/pcl